UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/945,360	08/31/2001	Anthony C. Chao	2100-0006	2865

23980 7590 12/18/2003

REED & EBERLE LLP
800 MENLO AVENUE, SUITE 210
MENLO PARK, CA 94025

EXAMINER
WALLENHORST, MAUREEN

ART UNIT	PAPER NUMBER
1743	

DATE MAILED: 12/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/945,360	CHAO ET AL.
	Examiner	Art Unit
	Maureen M. Wallenhorst	1743

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-63 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-63 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

2. The abstract of the disclosure is objected to because of the inclusion of legal phraseology such as "comprises". Correction is required. See MPEP § 608.01(b).

3. The disclosure is objected to because of the following informalities: On page 13, line 17 of the specification, Applicants are requested to provide the serial number of the application referenced here.

Appropriate correction is required.

4. Claims 36, 39-40, 43-47, 49-54 and 62-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 36 is indefinite since it is unclear how the recited fluid vessel is structurally related to the substrate having the plurality of test lanes thereon. It is unclear how the multiple fluids containing the different analytes are released from the fluid vessel recited in claim 36 to the substrate recited in claim 1. See this same problem in claim 44 with the recited "fluid vessel". It is not clear how this fluid vessel structurally cooperates with the substrate. Are the multiple fluids flowed through the cavity of the fluid vessel and then into the lanes on the substrate?

On line 2 of claim 39, the phrase "adapted to release" is indefinite since the recitation that an element is "adapted to" perform a function is not a positive limitation but only requires the ability to so perform. It does not constitute a limitation in any patentable sense. See In re Hutchison, 69 USPQ 138. See this same problem on line 3 of claim 40, on line 2 of claim 54, on line 3 of claim 62 and on line 3 of claim 63.

On line 1 of claim 43, the phrase "the means for detecting a change" lacks antecedent basis since claim 43 depends from claim 41, which does not positively recite this component of the device. Claim 43 should depend from claim 42 in order for this phrase to have proper antecedent basis.

Claim 45 is indefinite and incomplete since it is unclear where the flow passage is located in the device, and how it is structurally related to the other components of the device.

Claim 47 is indefinite since it is not clear what the substrate is detachable from.

In claim 49, the phrase "the substrate and cover plate surfaces" lacks antecedent basis.

5. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 1-38 and 41-61 are rejected under 35 U.S.C. 103(a) as being unpatentable over Socks et al in view of Takayama et al (submitted in the Information Disclosure Statement filed on February 6, 2002).

Socks et al teach of a method and device for conducting a cell-based analysis using laminar flow. The device 10 includes a substrate 12 made from an inert material such as glass. The device 10 also includes an optional cover plate 40 that is complementarily shaped with respect to the base 20 of the substrate. The cover plate 40 has first and second substantially planar opposing sidewalls at 42 and 44. Fluid-tight contact between the substrate 12 and the cover plate 40 is maintained so as to form a flow passage 50 there between. Located at the upstream end of the flow passage is a carrier fluid opening 52, and an outlet 54 is located at the downstream end of the flow passage. A target region 18 containing cells immobilized to the substrate surface is formed in the flow passage. Carrier fluid is introduced through the carrier fluid inlet 84 and maintained in contiguous laminar flow through the flow passage 50, over the target region 18 containing immobilized cells, and through the outlet. Preferably, the carrier

fluid is maintained in contiguous laminar flow at a constant volumetric flow rate and velocity. A stream containing a reagent can also be introduced through inlet 70 of an introduction tube 62 and into the carrier fluid while the carrier fluid is flowing through the flow passage 50. A plurality of introduction tubes 62 can be provided to introduce an analyte into the flow passage. This embodiment allows a plurality of analytes and/or reagents to be introduced into the carrier fluid to form lanes over the target region 18. Preferably, lanes of carrier fluid separate lanes of the reagent or analyte. The laminar flow ensures that the fluids do not mix and that each fluid lane is exposed to only a selected portion of the target region. The substrate and cover plate surfaces are typically located from 1 to about 500 micrometers from each other, more preferably from 20-100 micrometers. The substrate may consist of a glass slide. The device taught by Socks et al is intended for performing a cell-based assay, such as determining the effects of new reagents such as drugs on cells. In a cell-based assay, cells are immobilized on a portion of the target region 18 of the substrate such that the cells are downstream from the carrier fluid and analyte/reagent inlets. A stream containing an analyte is allowed to flow across the target region and contact the immobilized cells. The method further comprises determining whether the cells have caused a change to the analyte or whether the analyte has caused the cells to change. Preferably, the carrier fluid comprises a culture medium for sustaining the viability of the cells. Socks et al teach that both prokaryotic and eukaryotic cells can be used in the method. Preferably, the cells are primary cells obtained from a mammal. Preferred cell types include blood cells, endothelial cells, epithelial cells, liver cells, cardiac muscle cells, etc. The substrate surface on which the target region is located can be coated with a cell-adhering substance, such as collagen. The cell-adhering substance can be present as an array of features on the target

region when it is desired to provide an immobilized array of cells. The array can be any pattern such as lanes, checkerboards, spots or others so that cells may be spatially arranged at specific locations on the solid substrate surface. See paragraph 65 in Socks et al. If the cells are immobilized in an array, the array features and the fluid lanes of analyte/reagent must be aligned so as to effect precise delivery of the analyte/reagent to the cells. The immobilized cells are present on the target region as a monolayer. The biological activity of an analyte/reagent can be determined by visually observing changes or detecting changes in the substrate using a *microscope, a fluorescence detector, a radioactivity detector, etc.* The cell-based assays taught by Socks et al are useful for screening drug or drug candidates for a number of biological activities. In particular, the method allows for the ability to screen for the absorption, distribution, metabolism and/or excretion properties of an analyte. See paragraph no. 70 in Socks et al. Therefore, Socks et al teach of both a method and a device for conducting a multiplex assay such as is recited in the instant claims. However, Socks et al fail to specifically teach that the target region on the substrate contains a plurality of individual parallel lanes, each containing the same type of immobilized cells therein.

Takayama et al teach of a method for patterning cells using laminar fluid flow in microfluidic channels of a substrate. Cells are immobilized to the surfaces of the microfluidic channels in different patterns, i.e. in parallel stripes. See Figure 2A of Takayama et al where two different cell types are deposited into lanes or stripes next to each other. See also page 5548 of Takayama et al. Takayama et al teach that the patterns of cells inside the channels of a microfluidic device are useful for the study of the metabolism of the cells, and for screening compounds using the arrays of cells.

Based upon a combination of Socks et al and Takayama et al, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to formulate the target region on the substrate taught by Socks et al as parallel lanes of immobilized cells, such as taught by Takayama et al, since Socks et al provide the suggestion that patterns or arrays of cells (i.e. lanes) can be formed on the substrate in the target region by using patterns of a cell-adhering substance (i.e. collagen), and Takayama et al teach that parallel lanes or stripes of immobilized cells in the channels of a microfluidic device can be used to study the metabolism of cells and for the screening of compounds, which are the type of cell-based assays performed with the device taught by Socks et al. It also would have been obvious to one of ordinary skill in the art to flow the carrier fluid containing the analyte/reagent material in the method taught by Socks et al either parallel to or perpendicular to the lanes of immobilized cells on the substrate depending upon the desired amount of exposure and the desired degree of interaction between the immobilized cells and the analytes.

9. Claims 1-8, 11-36, 41-45 and 56-60 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bonde et al in view of Takayama et al (submitted in the Information Disclosure Statement filed on Feb. 6, 2002). For a teaching of Takayama et al, see previous paragraphs in this Office action.

Bonde et al teach of a flow cell assembly and cell-based assays using the assembly. The assembly comprises an open-faced chip or substrate made from glass or transparent plastic. The substrate contains thereon an analysis region wherein cells are immobilized. A hydrodynamically focused flow of a test liquid flanked by buffer flows of guidance liquids through respective inlet channels of the assembly are passed through the flow cell to an outlet on

the opposite side. In this way, the test fluid flows over the analysis region containing the immobilized cells. The interaction between the immobilized cells and the test liquid is observed with a microscope, a CCD camera, a means for detecting fluorescence, etc. The assembly taught by Bonde et al can be used to screen cells with respect to a selected analyte such as a potential new drug. This method comprises the steps of immobilizing cells on a solid surface, placing the surface in a housing adapted to provide a hydrodynamically focused stream of analyte over the immobilized cells, and flowing a hydrodynamically focused stream of analyte fluid over the immobilized cells, thereby allowing the analyte to contact the cells. The method further comprises determining a change in the cells or a change caused by the cells. Preferably, the hydrodynamically focused stream of fluid comprises a culture medium for sustaining the viability of the cells in addition to providing directionality to the stream of fluid containing the analyte. Both prokaryotic and eukaryotic cells can be used in the method. Preferably, the cells are primary cells obtained from a mammal such as blood cells, endothelial cells, liver cells, nerve cells, etc. The solid surface used in the method can be coated in a pattern with a material such as collagen that binds to cells so that a pattern (i.e. lanes, checkerboard, spots, etc.) of the cells is formed and spatially arranged on the surface. See paragraph no. 77 in Bonde et al. The hydrodynamically focused fluid is focused using guide streams to focus a central stream containing the analyte between two guiding streams, each introduced to the flow cell through its own inlet. Bonde et al also teach that the flow cell can be used to screen for the absorption, distribution, metabolism and excretion properties of analytes, such as potential drugs. See paragraph nos. 79-82 in Bonde et al. Bonde et al fail to specifically teach that the analysis region

on the chip or substrate contains a plurality of individual parallel lanes, each containing the same type of immobilized cells therein.

Based upon a combination of Bonde et al and Takayama et al, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to formulate the analysis region on the substrate taught by Bonde et al as parallel lanes of immobilized cells, such as taught by Takayama et al, since Bonde et al provide the suggestion that patterns or arrays of cells (i.e. lanes) can be formed on the substrate in the analysis region by using patterns of a cell-adhering substance (i.e. collagen), and Takayama et al teach that parallel lanes or stripes of immobilized cells in the channels of a microfluidic device can be used to study the metabolism of cells and for the screening of compounds, which are the type of cell-based assays performed with the device taught by Bonde et al. It also would have been obvious to one of ordinary skill in the art to flow the hydrodynamically focused fluid containing the analyte material in the method taught by Bonde et al either parallel to or perpendicular to the lanes of immobilized cells on the substrate depending upon the desired amount of exposure and the desired degree of interaction between the immobilized cells and the analytes.

10. Claims 39-40 and 62-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Socks et al in view of Takayama et al as applied to claims 1-38 and 41-61 above, and further in view of Parce et al. For a teaching of Socks et al and Takayama et al, see previous paragraphs in this Office action. Socks et al fail to teach that the analytes screened in the laminar flow device are present in a dry form on a matrix or matrices.

Parce et al teach of microfluidic devices wherein samples and reagents are flowed through microchannels in order to interact with one another in chemical/biological reactions.

Parce et al teach that the reagents and/or samples applied to the device can be present in a dry form on matrices. These samples/reagents are released from the matrices by contact with a carrier fluid that is flowed through the matrices into the channels of the microfluidic device. See lines 63-67 in column 30, lines 1-6 in column 31 and lines 1-12 in column 37 of Parce et al.

Based on the combination of Socks et al, Takayama et al and Parce et al, it would have been obvious to one of ordinary skill in the art to place the analytes screened in the cell-based assay taught by Socks et al onto dry matrices, similar to the reagents/samples used in the microfluidic device taught by Parce et al, so as to store these analytes in a stable form before use to prevent degradation or other loss prior to being screened in the cell-based assay, as taught by Parce et al.

11. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Please make note of: Scholz et al, Beyer et al, Lindemann et al, Duffy and Hamalainen et al who teach of different methods for assaying drug candidates for their absorption, distribution, metabolism and excretion properties.

Applicants are notified that in the Supplemental Information Disclosure Statement (IDS) received on January 18, 2002, the reference to WO 00/56444 is crossed out since this reference was already considered on the IDS received on February 6, 2002.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maureen M. Wallenhorst whose telephone number is 703-308-3912. The examiner can normally be reached on Monday-Wednesday from 6:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden, can be reached on 703-308-3912. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9310.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0661.

Maureen M. Wallenhorst
Primary Examiner
Art Unit 1743

mmw

December 15, 2003

Maureen M. Wallenhorst
MAUREEN M. WALLENHORST
PRIMARY EXAMINER
GROUP [redacted]1700